WARNING LETTER

Jon B. Cole, MD

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WARNING LETTER

Ref: 21-HFD-45-04-01

Dear Dr. Cole:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between April 10 and April 26, 2019. Investigator Kellie L. Thommes, representing FDA, reviewed your conduct of the following clinical investigations, which you performed as a sponsor-investigator:

• Protocol HSR 14-3841, “Ketamine vs. Haloperidol (Haldol) for Severe Agitation in the Pre-hospital Setting,” of the investigational drugs ketamine and haloperidol

• Protocol HSR 17-4306, "Ketamine vs. Midazolam (Versed) for Severe Agitation in the Pre-hospital Setting," of the investigational drugs ketamine and midazolam

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects have been protected.

At the conclusion of the inspection, Investigator Thommes presented and discussed with you the Form FDA 483, Inspectional Observations. We acknowledge receipt of your May 17, 2019, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your written response dated May 17, 2019, it appears that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

Failure to submit INDs for the conduct of clinical investigations with investigational new drugs subject to 21 CFR 312.2(a) [21 CFR 312.20 and 312.40(a)].

FDA regulations require a sponsor to submit, and to have in effect, an investigational new drug application (IND) before initiating a clinical investigation of a drug subject to 21 CFR 312.2(a) in human subjects, unless the clinical investigation qualifies for an exemption (see 21 CFR 312.20 and 312.40(a)). You failed to comply with these requirements. Specifically, you initiated and conducted the following clinical investigations of investigational drug products subject to section 505 of the Federal Food, Drug, and Cosmetic Act without submitting and having in effect an IND[1]:

• The clinical investigation of the investigational drugs ketamine and haloperidol, conducted under Protocol HSR 14-3841
• The clinical investigation of the investigational drugs ketamine and midazolam, conducted under Protocol HSR 17-4306

In your May 17, 2019, written response to the Form FDA 483, you stated that an IND was not needed for either Protocol HSR 14-3841 or Protocol HSR 17-4306 because the drugs administered in these clinical investigations were not research interventions. You argued that these

drugs were treatments, instead, that were administered according to the Emergency Medical System (EMS) treatment protocols and the clinical judgment of the Emergency Medical Technician-Paramedics (EMT-Ps). You stated that the EMT-Ps were free to use whichever therapy they thought was most appropriate, using their professional medical training. You stated that the EMT-Ps decided whether to sedate a subject and could choose not to enroll any particular subject in the investigations. You also stated that all three of the drug products were part of the standard of care used routinely by local EMT-Ps in the pre-hospital setting.

In the alternative, you argued that if the clinical investigations were subject to FDA jurisdiction, they met the criteria at 21 CFR 312.2(b)(1) for exemption from the requirements of part 312. You argued that the investigations met all five criteria for the exemption. With respect to the third criterion, you stated that the investigations did not involve a route of administration, dosage level, use in patient population, or other factor that significantly increases the risk or decreases the acceptability of the risk to subjects because the drugs were used "essentially in accord with their approved labeling" and were part of the local standard of care. You also stated in your response that the EMT-Ps were well-trained to care for the subjects receiving these drugs.

We address both of your arguments below.

1. *Protocols HSR 14-3841 and HSR 17-4306 were clinical investigations of drugs, as defined by 21 CFR 312.3(b).*

For purposes of 21 CFR part 312, a clinical investigation is defined as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part [312], an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice" [21 CFR 312.3(b)].

The clinical investigations conducted under Protocols HSR 14-3841 and HSR 17-4306 involved the administration of haloperidol and ketamine, and of ketamine and midazolam, respectively, to human subjects. Based on the information collected on inspection, Protocols HSR 14-3841 and HSR 17-4306 were designed to study the safety and efficacy of these drug products for the treatment of severe agitation, and severe agitation and profound agitation, respectively, in the pre-hospital setting.

The use of these drug products was not "in the course of medical practice." FDA has long held that when an investigator limits his choices, his patients' choices, and the choices of the people working for him in the treatment of those patients, then he is conducting a clinical investigation. This is different from the practice of medicine, where the primary intent is to treat the individual patient.[2]

Both protocols pre-specified the drug intervention to be administered to agitated subjects requiring chemical sedation during specified time periods. This was reinforced by removal of alternative treatment options from ambulances by your co-investigator, Dr. Jeffrey Ho, in his capacity as the Chief Medical Director for the Hennepin EMS, and by consistent communication from Dr. Ho and from you, the sponsor-investigator, to EMT-Ps regarding the specific drugs and dosages that were to be administered during particular time periods. As such, the clinical investigations limited the EMT-Ps' clinical judgment and limited the drug interventions that were available to the EMT-Ps for administration to each subject.

For example:

• Protocol HSR 14-3841 stated: "When the EMT-P's [sic] encounter a severely agitated patient in need of sedation for the first six months of the study[,] the patient will be given 10 mg of haloperidol IM; for the remaining six months[,] the patient will receive the standard dose of 5 mg/kg of ketamine IM." For Protocol HSR 14-3841, on January 15, 2015, you e-mailed EMT-Ps, stating: "We are still in the phase of the study where all [Altered Mental Status Scale] 2 & 3 patients are getting haloperidol, however [sic] at the end of January we plan to switch to the second phase of the study[,] and these patients will be receiving ketamine. There will be clear communication when the switch occurs to ketamine [emphasis removed]." Similarly, on February 1, 2015, you e-mailed EMT-Ps, stating: "Tomorrow, Feb [sic] 2 at 8:00 am [sic] we will be changing to the ketamine arm of the ketamine vs. haloperidol study . . . . [N]ow all patients who require chemical restraint for agitation (severe or profound) should receive ketamine 5 mg/kg intramuscularly . . . . So, to summarize, all patients with agitation . . . requiring chemical sedation that [sic] are being brought to H[ennepin] C[ounty] M[edical] C[enter] should receive ketamine 5 mg/kg IM." In this e-mail, you also indicated, "At this time haloperidol will be removed from the ambulances." Of note, one week after co-investigator Dr. Ho, in his capacity as Medical Director of Hennepin EMS, removed haloperidol

from the ambulances, EMT-Ps requested that haloperidol be returned to appropriately treat agitated patients who could not be enrolled in the study. Dr. Ho denied this request in a February 10, 2015, e-mail, copying you: "This is a study period[,] and the study is designed to determine the effect of 1 drug over another. Putting [haloperidol] back on the trucks during the period we are intentionally studying [k]etamine would dilute the number of potential subjects enrolled in the [k]etamine arm of the study."

• Protocol HSR 17-4306 stated: "In July of 2017, the Hennepin EMS standard operative procedure (SOP) for behavioral emergencies will change to ketamine as the first-line drug for both forms of agitation . . . . After a period of 6 months (January 2018), the SOP for behavioral emergencies will change to midazolam as the first-line drug for both forms of agitation . . . . When the EMT-P's [sic] encounter an agitated patient in need of sedation, for the first six months of the study patients with severe agitation . . . will receive 3 mg/kg IM ketamine (suggested max [sic] dose 250 mg) and 5 mg/kg ketamine IM (suggested maximum dose 500 mg) for profound agitation . . . . After a period of 6 months (January 2018), the SOP for behavioral emergencies will change to midazolam as the first-line drug for both forms of agitation, with 5 mg IM as the dose for severe agitation . . . and 15 mg IM as the dose for profound agitation." When the study conducted under Protocol HSR 17-4306 was first beginning, you e-mailed EMT-Ps on August 31, 2017, emphasizing that "the drug and dose have now changed to ketamine 3 mg/kg or 25 mg IM (instead of the previous [H]aldol/[V]ersed combo)." Further, the e-mail directed EMT-Ps to administer ketamine to patients as the first-line drug and to follow up with study enrollment. Similarly, on February 26, 2018, co-investigator Dr. Ho sent an e-mail stating: "On . . . February 12, we started the midazolam arm of our ketamine vs. midazolam study. As a quick reminder, all agitated patients start with midazolam as the initial drug, 5 mg IM for severe agitation and 15 mg for profound agitation." In addition, during the study, Dr. Ho had haloperidol removed from ambulances.

Consequently, the investigations conducted under Protocols HSR 14-3841 and HSR 17-4306 were clinical investigations of the investigational drugs ketamine and haloperidol, and of the investigational drugs ketamine and midazolam, respectively.[3] Under 21 CFR 312.20 and 312.40, you were required to submit and to have in effect INDs before initiating these clinical investigations.

Your statements that the drugs studied in Protocol HSR 14-3841 and Protocol HSR 17-4306 were not investigational drugs are not persuasive because they are inconsistent with the design and conduct of the clinical investigations. The clinical investigations involved the prospective administration of specific drug products depending on the date of administration, the assessment and documentation of time to sedation, and the comparison of times to sedation among different drugs where the investigational drug was the independent variable of primary interest. Contrary to your assertions, both clinical trials required the EMT-Ps to administer a specific investigational drug to agitated subjects who were to be sedated chemically. Whether a severely agitated subject in need of sedation received either ketamine or haloperidol while Protocol HSR 14-3841 was ongoing, or whether a severely or profoundly agitated subject in need of sedation received either ketamine or midazolam while Protocol 17-4306 was ongoing, depended not on the clinical judgment of the EMT-Ps but on the date the EMT-Ps encountered the subject. In addition, the presence of the choice not to enroll any particular subject is common in clinical investigations and does not support your assertion that the drug products were not investigational new drugs with regard to subjects who were enrolled. Finally, the fact that the drugs individually can be part of standard of care does not render them non-interventions in the study setting, as was the case here, where the protocols pre-specified the drug intervention that would be administered to agitated subjects requiring chemical sedation and limited both the EMT-Ps' clinical judgment and the interventions that were available to EMT-Ps for administration to each subject.

2. *The clinical investigations conducted under Protocols HSR 14-3841 and HSR 17-4306 are subject to the IND regulations under 21 CFR 312.2 and do not meet the exemption criteria under 21 CFR 312.2(b)(1).*

As noted above, FDA regulations require a sponsor to submit an IND before conducting a clinical investigation of a drug in human subjects, unless the clinical investigation qualifies for an IND exemption under 21 CFR 312.2(b). Under 21 CFR 312.2(b)(1), the clinical investigation of a lawfully marketed drug product in the United States is exempt from the IND regulations for a clinical investigation if **all** of the following exemption criteria are met:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use and there is no intent to use the investigation to support any other significant change in the labeling of the drug.

2. In the case of a lawfully marketed prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

3. The investigation does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

4. The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56, and with the requirements for informed consent set forth in 21 CFR part 50.

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

Your use of the investigational drugs (ketamine, haloperidol, and midazolam) in the clinical investigations conducted under Protocols HSR 14-3841 and HSR 17-4306 did not qualify for the exemption at 21 CFR 312.2(b)(1). For example, these investigations did not satisfy the third exemption criterion above, found at 21 CFR 312.2(b)(1)(iii). That is to say, the investigations significantly increased the risks (or decreased the acceptability of the risks) associated with the use of the drug products.

Here, the clinical investigations conducted under Protocols HSR 14-3841 and HSR 17-4306 involved factors that significantly increased the risks (or decreased the acceptability of the risks) associated with the use of the drug products. First, Protocols HSR 14-3841 and HSR 17-4306 lacked an acceptable method for excluding pregnant women and pediatric patients, thus significantly increasing the risk with respect to those vulnerable study populations. Also, neither Protocol HSR 14-3841 nor Protocol HSR 17-4306 excluded subjects who were under the influence of intoxicants, in whom the use of ketamine is cautioned, nor did they provide precautions to better ensure the safety of these subjects. In addition, your protocols lacked specific measures to

sufficiently guarantee the safety of study participants in the pre-hospital setting. Therefore, these clinical investigations failed to meet the exemption criteria under 21 CFR 312.2(b)(1)(iii).

We note that on May 15, 2014, you submitted IND 122826 for the investigational drugs ketamine and haloperidol in order to conduct a clinical trial that would have been substantially similar to the trial you sponsored and conducted under Protocol HSR 14-3841. You withdrew this IND following a June 10, 2014, teleconference with the Division of Psychiatry Products (DPP), during which DPP conveyed deficiencies with respect to your IND. These deficiencies were also shared with you in writing following the teleconference. Among other things, DPP informed you that excluding "obviously gravid women" was not an acceptable or the standard method of exclusion of pregnant women in a trial. DPP also informed you that excluding subjects who "appear to be less than 18 years old" was not a reliable method to exclude pediatric patients, and that your protocol should include a reliable method to guarantee the exclusion of pediatric patients. In addition, DPP noted that ketamine labeling provides that caution should be used in the chronic alcoholic and the acutely alcohol-intoxicated patient, and that agitated patients in the pre-hospital setting run a high risk of being under the influence of various intoxicants. DPP recommended that you consider excluding from your study patients under the influence of various intoxicants. Finally, DPP noted ketamine labeling provides that ketamine should be used by or under the direction of physicians experienced in administering general anesthetics and in the maintenance of an airway and in the control of respiration, and that measures to guarantee the safety of study participants, including, for example, management of possible laryngospasm in a pre-hospital setting, should be clearly described in the protocol, given the ketamine safety profile.

Instead of addressing these deficiencies, you proceeded with a substantially similar clinical investigation of the investigational drugs ketamine and haloperidol under Protocol HSR 14-3841, and a follow-up trial of investigational drugs ketamine and midazolam under Protocol HSR 17-4306, without submitting or having in effect an IND. Moreover, neither Protocol HSR 14-3841 nor HSR 17-4306 addressed the concerns that DPP communicated to you. The studies conducted under Protocols HSR 14-3841 and HSR 17-4306 significantly increased the risks and/or

decreased the acceptability of the risks to subjects associated with the use of the investigational drug products in several ways that DPP had specifically identified.

First, both protocols excluded "obviously gravid women, persons known to be less than 18 years old, and persons who obviously appear to be less than 18 years old." As DPP informed you, these are not acceptable, standard, or reliable methods for excluding pregnant women and children from clinical investigations. As a result, one pregnant woman was enrolled in Protocol HSR 14-3841, and two children under the age of 18 were enrolled in Protocol HSR 17-4306. Administration of the investigational drugs to these subjects placed them at significantly increased risk of the adverse events associated with the investigational products and decreased the acceptability of those risks.

Second, in both protocols you specifically noted that agitated patients who require sedation in the EMS setting "are frequently under the influence of drugs and/or ethanol." Despite these acknowledgments, the precaution included in the ketamine labeling, and DPP's concerns, you did not exclude subjects under the influence of intoxicants from either study, nor did you include any precautions for subjects under the influence of such intoxicants in your protocols. According to the published results for Protocol HSR 14-3841, the presenting Emergency Department median breath alcohol levels were 120 mg/dL in the ketamine group (n=23) and 160 mg/dL in the haloperidol group (n=70). Median serum alcohol levels were 220 mg/dL in the ketamine group (n=27). According to the published results of a urine drug screen performed on 37 of the 146 subjects enrolled in Protocol HSR 14-3841, four subjects tested positive for benzodiazepines and four subjects tested positive for opioids, specifically fentanyl, hydrocodone, and oxycodone. According to the published interim analysis of Protocol HSR 17-4306, the etiology of agitation was alcohol in 203 study subjects then enrolled (69%), with a median alcohol concentration of 220 mg/dL. The etiology of agitation was suspected drug intoxication in 133 study subjects then enrolled (38%). Your failure to exclude, and the lack of any precautions for, subjects under the influence of various intoxicants significantly increased the risks and/or decreased the acceptability of the risks associated with the investigational drugs.

Third, despite DPP's cautioning that ketamine should be used by or under the direction of physicians experienced in the maintenance of an airway and in the control of respiration, and that measures to guarantee

the safety of study participants, including the management of possible laryngospasm in the pre-hospital setting, should be clearly described in the protocol, you conducted both studies in the pre-hospital setting and did not put in place any specific measures to protect study participants. According to the published results of Protocol HSR 14-3841, the intubation rate was significantly higher in the ketamine group, with 39% of subjects (25 out of 64) who received ketamine being intubated vs. 4% of subjects (3 out of 82) who received haloperidol being intubated. According to the published interim results of Protocol HSR 17-4306, 31% of subjects (20 out of 65) receiving ketamine 5 mg/kg were intubated, and 22% of subjects (31 out of 138) receiving ketamine 3 mg/kg were intubated. The failure to take any specific safety precautions for the administration of ketamine in the pre-hospital setting when conducting clinical investigations significantly increased the risks associated with the use of this product.

Because the administration of the investigational drugs (ketamine, haloperidol, and midazolam) in these clinical investigations significantly increased the risks and/or decreased the acceptability of the risks associated with the use of these drug products, the exemption criterion at 21 CFR 312.2(b)(1)(iii) was not met, and you were required to submit and have in effect INDs before initiating these clinical investigations.

In your May 17, 2019 response, you stated that use of the investigational drugs did not significantly increase the risk or decrease the acceptability of the risk to subjects because the drugs were used “essentially in accord with their approved labeling.” Your statement is factually incorrect, because none of the three drugs used in Protocols HSR 14-3841 and HSR 17-4306 is indicated to treat severe agitation or profound agitation. In any case, your response did not address the fact that the studies significantly increased the risks and/or decreased the acceptability of the risks to subjects associated with use of the drug products because you did not have appropriate methods to exclude subjects and did not have measures in place to sufficiently guarantee the safety of study participants in the pre-hospital setting.

You also stated in your response that the investigational drugs were part of the local standard of care and that the EMT-Ps were trained to properly evaluate, treat, and monitor their patients. You specifically noted that the EMT-Ps were trained and experienced in maintaining a patient’s airway, supporting ventilation, and continuous monitoring of patients who receive these drugs. These assertions, however, do not

change the fact that the clinical investigations, by failing to exclude study subjects at significantly increased risk from administration of the investigational drugs, or by failing to have in place specific measures to sufficiently guarantee the safety of subjects in the pre-hospital setting, significantly increased the risks and/or decreased the acceptability of the risks to subjects.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies comply with FDA regulations.

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. Within 15 business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately address this matter may lead to regulatory action. If you believe you have complied with the Federal Food, Drug, and Cosmetic Act and FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Sherry G. Bous, Pharm.D., at 240-402-8176 or CDER-OSI-Communications@fda.hhs.gov. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,
/S/
David C. Burrow, Pharm.D., J.D.
Director

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1 Also, neither of these clinical investigations qualified for any of the exemptions listed at 21 CFR 312.2 from the application of 21 CFR part 312. Because you have argued that these clinical investigations were subject to the exemption provided at 21 CFR 312.2(b)(1), we discuss in more detail below the inapplicability of this provision to these clinical investigations.

2 Indeed, FDA has provided guidance on this topic. See FDA's guidance to industry *Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND* (published in September 2013) at 4, 15 ("For example, a randomized trial evaluating an unapproved use of a lawfully marketed drug is a clinical investigation and may require an IND. In contrast, use of a lawfully marketed drug for an unapproved use in the course of medical practice is not a clinical investigation and does not require an IND because it involves the use in an individual patient where the primary intent is to treat the patient").

3 We note that, for the same reason, these clinical investigations do not qualify for the exemption from the application of 21 CFR part 312 provided at 21 CFR 312.2(d).